



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket #: 45010-00601

DECLARATION OF Stuart A. Newman, Ph.D

Stuart A. Newman declares as follows:

1. I am employed by New York Medical College as a
_____. My business address is Dept Cell Biology + Anatomy, NYMC
Valhalla NY
My home address is 23 Frognois Rd Pleasantville NY 10570
2. I have been employed by New York Medical Coll since 1979.
3. I have worked in the area of Developmental Biology since 1971.
4. I did my undergraduate work at Columbia Univ. and was awarded the AB degree in
1965 (year).
5. I received a PhD degree in Chemistry from Univ. of Chicago in
1970 (year). Following that training, I did post-graduate work at Univ. of Sussex, UK
During that time I worked in the area of developmental biology. I have had extensive

training and practical experience in the area of developmental biology. I am familiar with and understand the scientific literature in this area.

6. Based upon my training and experience I am familiar with the level of knowledge of one of ordinary skill in the art. The invention relates to the field of biology, and in particular the field of developmental biology. In this field of study, one of ordinary skill in the art would hold a Doctor of Philosophy degree and possess at least two years of post-doctoral training.

7. I have reviewed the above-referenced U.S. Patent Application and the United States Patent and Trademark Office's ("PTO") rejection of the application.

8. It is my understanding that the PTO has taken the position that the specification fails to provide an enabling disclosure for how to make and use the chimeric embryos of the invention.

9. Published literature describes, in detail, specific technologies for creating intra- and interspecific embryo chimeras, establishing that the techniques are not only well known, but readily available, understood, and used by researchers of ordinary skill in the art for a wide variety of investigations.

10. Based upon my training and experience it is my understanding that the methods for making intraspecific mammalian chimeras (e.g., tetraparental mice) have been disclosed in the literature since the 1960's. (Miniz, B., and Baker, W. W. (1967). Normal Mammalian Muscle Differentiation and Gene Control of Isocitrate Dehydrogenase Synthesis. *Proc Natl Acad Sci USA* 58, 592-8). These methods are well known in the field of mammalian embryology.

11. Based upon my training and experience it is my understanding that the methods for making interspecific mammalian chimeras (between mouse and rat or between two species of mouse), have been disclosed in the literature since the 1970's and 1980's, respectively. Interspecific chimeras were created using the techniques originally developed for intraspecific mammalian

chimeras (the mixing of embryonic cells from two different species). (Stern, M. S. (1973) Chimacras Obtained by Aggregation of Mouse Eggs with Rat Eggs. *Nature* 243, 472-3; Rossant, J., Croy, B. A., Chapman, V. M., Siracusa, L., and Clark, D. A. (1982) Interspecific Chimeras in Mammals: a New Experimental System. *J Anim Sci* 55, 1241-8).

12. Techniques developed for the production of interspecific mouse-mouse chimeras (Gardner, R. L. (1968) Mouse Chimeras Obtained by the Injection of Cells into the Blastocyst. *Nature* 220, 596-7) were used to produce sheep-goat chimeric embryos. Techniques to produce sheep-goat chimeras by embryo manipulation and the use of interspecific chimerism to allow successful interspecific embryo transplantation in sheep and goats are well known in the literature (Fehilly, C. B., Willadsen, S. M., and Tucker, E. M. (1984) Interspecific Chimaerism Between Sheep and Goat. *Nature* 307, 634-6) and known and understood by those of ordinary skill in the art.

13. It was known to one of ordinary skill in the art that the technology for producing chimeric mammalian embryos may be insensitive to variations in procedure or species origin of the cells. Techniques developed for mouse embryo culture, sheep embryo culture, mouse-mouse, and mouse-rat chimeras, have all proved successful for sheep-goat chimera production.

14. One of ordinary skill in the art would not anticipate that use of a different mammalian species, such as the human, would require "undue experimentation" for the design of a protocol for producing chimeras. Rather, many available references reflect the utility of these techniques across species. As such, one of ordinary skill in the art would understand that the use of techniques in one species can be used in similar or closely related species.

15. By studying the available literature, the present invention would be adequately enabled to one of ordinary skill in the art.

16. It is my understanding that the PTO has taken the position that the outcome of how to make and use chimeric embryos composed of cells from both human and non-human mammals is unpredictable and is not entitled to patent protection.

17. All biotechnological procedures inherently lead to unpredictable outcomes. Genetic and other uncontrolled biological variability of organisms necessarily make outcomes unpredictable.

18. This unpredictability is well known to those of ordinary skill in the art. Variability of outcome is one of the useful aspects of the human/non-human chimera as a research tool.

19. It is my understanding that the PTO has taken the position that the creation of a human/non-human embryo would be obvious to one of ordinary skill in the art.

20. Although the techniques for creating intra- and interspecific chimeric embryos are known, this field of science is unpredictable, and as such the above-referenced invention is not obvious.

21. The references set forth by the PTO fairly and correctly characterize what is known in the art.

22. In spite of the references there are differences in the invention claimed in the above-referenced application. I am unaware of any instance of this invention being made, taught, or suggested by the references. The invention as a whole would not be obvious to one of ordinary skill in the art.

23. The ability to construct chimeras has only recently become possible due to advances in technology. The available scientific literature known to those of ordinary skill in the art would not, either alone or in combination, anticipate or obviate the human/non-human chimeric embryo invention.

24. The patentability of the human/non-human embryo is evidenced by the fact that, despite numerous publications containing ample teachings of the techniques disclosed, the field of the

invention remains so complex and unpredictable that one of ordinary skill in the art would not have known, or considered obvious, the claimed invention.

25. Consequently, based upon these facts, and my training and experience, the scientific literature would enable one of ordinary skill in the art to create the human/non-human embryos of the claimed invention, but would not render the creation of a human/non-human chimera obvious.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on: June 15, 1999

(Signature) Stuart A. Newman

NAME (Printed) Stuart A. Newman